UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/843,922 | 04/30/2001 | Masayuki Fukumura | 4001-0003CIP | 2336 |

7590 05/05/2004

Mark R. Shanks
REED SMITH LLP
1301 K Street NW
Suite 1100 East Tower
Washington, DC 20005-3373

| EXAMINER | |
|---|---|
| KELLY, ROBERT M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/843,922 | FUKUMURA ET AL. | |
| | Examiner | Art Unit | |
| | Robert M Kelly | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6,8-13,15 and 16* is/are pending in the application.

4a) Of the above claim(s) *12 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-11,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/22/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response to restriction requirement and preliminary amendment, received 29 March 2004 has been received and entered.

Claims 7 and 14 have been canceled.

Claims 1-6, 8-13, and 15-16 are pending.

### *Election/Restrictions*

Claims 12-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Applicant's Response to Restriction Requirement, received 29 March 2004.

### *Double Patenting*

**Note: The examiner was unable to obtain a copy of the issued patent for his analysis, but was able to obtain a copy of the allowed claims and a copy of a pregrant publication from the same application, U.S. Pregrant Publication No.: US 2002/0100066. Therefore, although unlikely, the actual claim numbers of the issued patent may be different.**

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 16 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 2, 8, and 9 of prior U.S. Patent No. 6,723,532, filed 30 April 1998, patented 20 April 2004. This is a double patenting rejection.

Claim 16 of the instant application is drawn to any paramyxoviridae virus vector. Moreover, the intended use of the virus is not considered limiting to claims products.

Claims 1-2 of U.S. Patent No. 6,723,532 encompass a complex devoid of helper virus, which is produced by injecting a Sendai virus RNA molecule (Sendai virus is one member of the family paramyxoviridae) comprising any foreign gene into a cell that expresses viral structural components essential for autonomous replication of Sendai virus, which RNA has at least one gene of the group M, F, and HN deleted or inactivated, thereby providing a complex with cell infectivity and autonomous replication ability but no ability to disseminate. Claim 2 limits the cell's expressed viral structural components to comprising NP and RNA polymerase proteins derived or isolated from Sendai virus. Claims 9 and 11 of U.S. Patent No. 6,723,938 encompass methods for producing dissemination deficient yet replication and infection competent Sendai viral particles, which comprises the steps of introducing the complexes (virus vectors) of Claim 1 into packaging cells, which express the deleted genes of the complex. Claim 11 requires that such cells do not express heterologous RNA polymerase. Furthermore, it is clear from the specification of the pregrant publication that such complex is a Sendai virus vector (pregrant publication, p. 6, paragraphs 0110-0114).

Hence Claims 1-2 of U.S. Patent No. 6,723,938 encompass one of the family of vectors encompassed by claim 16 of the present application, and the methods of Claims 9 and 11 of U.S. Patent No. 6,723,938 encompass methods which result in the production of such vectors.

Therefore, the claims listed encompass common subject matter.

**The Examiner was unable to obtain a current copy of the claims in the Application below. Therefore this rejection is also provisional because Applicants may have amended the claims from those listed below, as reflected in the Pregrant Publication that has issued from this Application, Publication No.: US 2002/0098576. However, Applicants are forewarned that upon receipt of a copy of the current claims, following office actions may contain further rejections vis a vis this Application.**

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 16 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 09/728,207. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claim 16 of the instant application is drawn to any negative strand RNA virus, and Claims 1-3 of copending Application No. 09/728,207 encompass one such virus vector, Sendai virus vectors, comprising deletions of endogenous genes or insertions of exogenous genes. Therefore these claims encompass common subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 16 is provisionally rejected under the judicially created doctrine of double patenting over claims 1-3 of copending Application No. 09/720,003. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: Claim 16 of the instant application is drawn to any negative strand RNA virus. Claims 1-3 of copending Application No. 09/720,003 are drawn to the subset of negative strand RNA viruses that are sendai viruses comprising insertions, deletions, or gene inactivations that do not remove the disseminative capacity of the virus. Hence Claim 16 of the instant application encompasses all of Claims 1-3 of copending Application No. 09/720,003.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 8-11, and 15-16 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-6, 8-10, and 14-18 of copending Application No. 09/720,979. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

Claim 1 of the instant application is drawn to methods of local delivery of negative strand RNA viruses to mammalian nerve cells comprising contacting the cells with the virus or cells

comprising the virus. Claims 1 and 16-18 of copending Application No. 09/720,979 are drawn to similar methods of delivery, but encompassing all nerve cells, intraventricular administration, administration to the brain parenchyma, and use of a transgene for regulating food intake, respectively. Hence Claim 1 of the instant Application is encompassed by Claim 1 of copending Application No. 09/720,979, and Claims 16-17 encompass specific methods of administration of Claim 1 of the instant Application.

Claims 2-6, 8-9 and 11-16 are drawn to the same subject matter as Claims 2-6, 8-10, and 14-15 of copending Application No. 09/720,979. They also have the same dependencies from Claim 1 of their specific applications (See above). Hence, the claims encompass the same subject matter, and copending Application No. 09/720,979 encompasses the subject matter of Claims 2-6, 8-9 and 11-16 of the instant application.

Claim 11 of the instant application encompasses all neurotrophic protein encoding genes, which is encompassed by Claims 1 and 5, and specific species of neurotrophic genes are listed in Claim 10 of copending Application No. 09/720,979. Hence Claim 11 of the instant application encompasses similar subject matter to the aforementioned claims in copending Application No. 09/720,979.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 16 is provisionally rejected under the judicially created doctrine of double patenting over claim 1 of copending Application No. 10/444,661. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: Claim 16 is drawn to any paramyxoviridae virus vector. Claim 1 of copending Application No. 10/444,661 is drawn to any paramyxoviridae virus vector comprising any angiogenic trangene. Hence, Claim 16 of the instant Application encompasses Claim 1 of copending Application No. 10/444,661.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

***Priority***

If applicant desires priority under 35 U.S.C. 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or

120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1-6, 8-11, and 15-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The addition of the term "local delivery" in claims 1 and 16, as amended in Applicant's second amendment received 29 March 2004 is considered new matter. Support for the amendments has not been provided with Applicant's second amendment received 29 March 2004, and no support can be found in the specification as originally filed. Claims 2-6, 8-11, and 15 each depend from Claim 1 and comprise the same scope.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of Claims 9-10 encompass proteins capable of protecting the brain from ischemia and neurotrophic factors.

These agents of these claims are broad in scope, being defined on the basis of their effect, and not on any specific structure. The specification broadly discloses GDNF (e.g., p. 2), FGFs,

nerve growth factors, apoptosis inhibitors, heat shock proteins, peroxidases, neurotrophic factors and eleven examples of these various proteins (p. 10).

In analyzing whether the written description requirement is met for gene claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, although some specific examples above are known in the art by structure, such is not enough to allow one to distinguish the various members of each of the genera from one another. The specification does not provide any disclosure as to what would have been the required structure which would allow one to distinguish the various species of the genera and there is no disclosure as to what is the common structure of the members of the genus that would protect the brain from ischemia or would be a neurotrophic factor. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other characteristics are that the proteins act as neurotrophic factors or protect the brain from ischemia or other neural degeneration (p. 10).

Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera from each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of

> particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any neurotrophic factor or any protein that protects the brain from ischemia, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8-11, and 15-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(i) a method of delivery of a nucleic acid sequence to mammlian nerve cells *in vitro* comprising a step of contacting such cells with a Sendai viral vector comprising the nucleic acid sequence to be delivered, which nucleic acid sequence is inserted between the R1 and R2 locuses of the Sendai viral vector, and

(ii) a method of delivering a nucleic acid sequence encoding a protein to rodent nerve cells *in vivo* comprising the direct administration of a Sendai viral vector comprising such sequences between the R1 and R2 locuses of the vector to the nerve cells, by direct injection, wherein the transgene is expressed, thereby causing expression of the transgene,

does not reasonably provide enablement for any method of administration, any viral vector, any ex vivo method, transgenes located in any part of the viral genome, or the treatment of any mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its fully claimed scope, and that, therefore, Applicant's claims are not enabled to their fully claimed scope.

**The Breadth of the Claims**

Claims 1-6, 8-11, and 15-16 are broad in scope. The following paragraphs will outline the full breadth of these claims.

Claims 1-6 and 8-11 encompass methods for the delivery of any nucleic acid sequence to any mammalian nerve cells, comprising contacting the nerve cells with either any paramyxoviridae virus vector or any cell comprising such virus vector. Claim 2 limits the nerve cells to any central nervous system (CNS) cells. Claim 3 limits the CNS cells to any ventricular ependymal cells. Claim 4 limits the CNS cells to any hippocampus cells. Claim 5 limits the vector to comprising any foreign (to the virus) gene. Claim 6 limits the transformed cells to transiently expressing the foreign gene. Claim 8 limits the foreign gene to encoding a protein that acts on any hypothalamic nuclei. Claim 9 limits the foreign gene to encoding any protein that is capable of protecting the brain from ischemia. Claim 10 limits the protein of Claim 9 to any neurotrophic factor. Claim 11 limits the foreign gene of Claim 5 to one of twelve growth factor genes. Claim 15 limits the viral vector to being derived from Sendai virus.

Claim 16 is encompasses any paramyxoviridae virus vector.

Because these claims are broad, encompassing *in vitro*, *in vivo*, and *ex vivo* transformation of cells using a wide variety of virus vectors, with or without foreign genes, to transform a wide variety of mammalian cells, as well as the transformation of any mammalian nerve cell with any cell, xenogenic, allogenic, or autogenic, that has been transformed with the vector, and via any method of administration, the detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide area of knowledge, to a reasonably comprehensive extent. In other words, each of those aspects considered broad must be fleshed

out to a reasonable extent so that one of ordinary skill in the art at the time of invention by Applicant (hereinafter the "Artisan"), would be able to practice the invention, and do so to the fully-claimed scope of invention, without an undue burden being imposed on such Artisan (undue burden). However, as will be discussed below, this burden has not been met.

**The Nature of the Invention**

The invention, when viewed from the perspective of the specification, is in the nature of gene therapy for nervous system disorders (pp. 1-4). Gene therapy is generally not enabling of any new invention in the field.

With regard to gene therapy, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. For example, Deonarain (1998) Expert Opin. Ther. Pat., 8: 53-69, indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequeate levels for a long enough period of time" (p. 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (p. 65, CONCLUSION). Verma (1997) Nature, 389: 239-242, reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (p. 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on

here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression ... The use of viruses (viral vectors) is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3).

Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, are all important factors for a successful gene therapy (e.g., bridging pp. 81-82). In addition, Gorecki (2001) Expert Opin. Emerging Drugs 6(2): 187-98) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g., ABSTRACT).

Furthermore, on top of the obstacles to mentioned above with respect to any gene therapy invention, Gene therapy is also generally not enabling of the transfer of any particular technique between species.

Crystal (1995) Science, 270: 404-410, provides a long list of clinical trials that have yet to yield therapeutic benefits and further states that "humans are not simply large mice." (p. 409). Further underscoring the point that Crystal made, Gura (1997) Science, 278: 1041-42 states, "the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all." Gura states that they had "basically discovered compounds that were good mouse drugs rather than good human drugs." (p. 1041). Thus, the Artisan could only conclude from any successful results that the method would only work in that particular animal type used, and would not necessarily be efficacious in other animals, such as humans.

Lastly, gene therapy is generally not enabling for the use of any vector, even when such vectors are within the same family or subfamily, particularly when the paramyxoviridae viruses are concerned, because the Artisan would not know where in the genome to place any specific transgene to obtain enough expression for a long enough period of time to have a desired effect.

To wit, Lamb, et al. (2001) Fundamental Virology, 4$^{th}$ Ed., by Lippincott, Williams, and Wilkins, New York, NY., p. 691, points out that the distance from the 3' end of the genome effects how much transcription of any particular gene will take place, and that such is influenced by the size and length of the polyA tails after each gene. Hence, the Artisan could not reasonably predict that any particular location in the genome would produce enough stable and functional mRNA to produce enough of an effect for a long enough period of time to effect treatment. Moreover, because each of these viruses are different, having different genes and gene lengths in different orders and different polyA tail lengths, these effects would not be expected to exactly correlate between each virus, further obscuring any *a priori* conclusions an Artisan might draw with regard to any specific species. Moreover, the insertion of such a

transgene into a particular virus may attenuate important gene transcription for viral genes, and thereby make the virus that was constructed no longer replicate, and therefore, unable to be manufactured. The only conclusion that an Artisan could draw, therefore, with regard to any specific vector is that the vector works for that specific vector, and not necessarily for any other vector derived from any virus of the paramyxoviridae family.

In reviewing the above-discussed problems, it is clear that the Artisan would therefore require, to make and/or use a new invention in the field, a showing that enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such occurs for a long enough period of time to effect treatment.

Moreover, to extrapolate to other species, the Artisan would require a showing that would allow him or her to reasonably predict that the methods would work in other species. For example, while a showing a few different species of one phylogenic genus may enable that genus, it would be much less likely to enable the whole phylogenic kingdom to which the genus belongs. Also, to extrapolate to the use of other vectors, the Artisan would require a showing that any particular vector could target and transform enough cells, and express enough protein therefrom, to effect any particular treatment. Alternatively, direct examples of such vectors and species being used and treated, respectively, would overcome such showing as if the protocols were successful, the methods and vectors must have met the requirements.

**The State of the Prior Art**

The state of the prior art with regard to the paramyxoviridae viruses and the use in transforming neural cells is similarly not enabling of new inventions in the field. While no art of record demonstrates the use of any paramyxoviridae vectors for transforming neural cells, there does exist scant art for the use of sendai viruses in vascular disease and the use of sendai viruses in the form of fusogenic liposomes for the delivery of genes.

Yonemitsu, et al. (2002) Surgery, 131(Supp.1): S261-S268 describes the use of sendai virus vectors in vascular surgery. In Yonemitsu, he echoes some of the concerns addressed in the nature of the invention, above, stating, with regard to previous gene therapy studies, "there are still unsolved issues; the efficacy of these studies largely depends on the gene-transfer efficiency ... The majority of these studies were performed using virus based vectors, and diseased human vasculature possesses several biological barriers to limit gene-transfer efficiency. In fact, gene-transfer efficiencies of adenoviral vectors and recombinant Sendai virus vector were markedly decreased by atherosclerosis or fibromuscular neointima ... the extracellular matrix might thus play a critical role in limiting gene transfer." (p. S262). Essentially, Yonemitsu is recognizing the targeting problem, and that this problem can often be exacerbated when a disease state is present due to histological changes in the tissues. Continuing with his discussion, Yonemitsu further demonstrates that even though VEGF is known to help with angiogenesis, gene therapy to effect the production of VEGF to increase angiogenesis has "many unsolved issues related to the biologica actions of angiogenic growth factors and therapeutic outcome need to be clarified." Again, Yonemitsu recognizes that the use of such vectors is not predictable, even in the face of expressing a protein known to be effective. Yonemitsu concludes by demonstrating some optimism, but a recognition that many problems

still need to addressed in order to develop a gene therapy protocol using, *inter alia*, Sendai viral vectors (p. 266). Hence, Yonemitsu, though not even addressing the neural systems of Applicant's invention, evinces many of the same concerns about gene therapy as the nature of the invention. Therefore, the Artisan would not find Yonemitsu enabling of Applicant's invention, drawn to a different tissue and many forms of therapy.

Nakanishi, et al. (1999) Mol. Membr. Biol., 16: 123-27 is similarly not enabling of Applicants invention. Nakanishi provides the use of fusogenic liposomes, the fusion of a sendai virus and a simple liposome to effect gene therapy (p. 123). However, these liposomes are not as fusogenic as ordinary Sendai virus (p. 124). Hence, the Artisan could not reasonably predict from Nakanishi that any Sendai virus would act similarly to the fusogenic liposomes, as far as any targeting were concerned. Moreover, Nakanishi recognizes that the system designed needs further improvements before it will be useful for treating metabolic disorders (p. 126). Hence, even though Nakanishi doesn't even propose applicant's vectors, Nakanishi demonstrates that any Sendai virus vector, even if designed for better vector targeting, is not generally enabled by the state of the art.

Hence, the state of the prior art contributes nothing over that of the nature of the invention, and the same questions and concerns would still exist in the Artisans mind. Therefore, absent a strong disclosure by way of specific guidance and direction and/or working example, by the Applicant, the invention is not enabled for its fully claimed scope.

**The Level of One of Ordinary Skill in the Art at the Time of Invention**

The level of one of skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its

unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed to its fully-claimed scope without undue experimentation.

**The Level of Predictability in the Art**

Because the art, as shown above, does not disclose any predictable use of sendai vectors *in vivo*, no use of *ex vivo* transformed sendai vectors, no other vectors of the family paramyxoviridae, or the reasonably predictable treatment of multiple species with the same transgene and vector, the Artisan could not predict, in the absence of proof to the contrary, that such applications would be efficacious in any therapeutic application.

Hence, absent a strong showing of guidance and direction and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for its fully claimed scope.

**The Amount of Direction and Guidance Provided by Applicant**

The specification broadly discusses gene therapy for neurodegenerative disease, viral vectors, and neurotrophic factors (pp. 1-3), a disclosure of the invention generally tracking the claims (pp. 3-5), definitions, descriptions of the sendai virus and vectors therefrom (pp. 6-8), transgenes, ischemia, and vector administration methods (pp. 8-11), and a brief description of the drawing (pp. 11-12). Moreover, it is noted with regard to placement of any transgenes into the sendai virus vector that Applicant only discloses that such transgene are preferably placed between the R1 and R2 sequences (p. 7).

Such broad description does not, however, consititute the specific guidance and direction that the Artisan would require to reasonably predict that any paramyxoviridae virus could be

used, that any transgene could produce an effect, that *ex vivo* treatment would be efficacious, that any mammal could be treated, that any route of administration would be effective, that any location within the genome would be useful for inserting transgenes, or that any neurodegenerative disease could be treated.

Because of the lack of specific guidance and direction that would assure the Artisan of that such treatments and vectors would be efficacious, the examples would be required to provide a very strong showing of effectiveness. Absent this strong showing in the examples, it would have required undue experimentation to make and/or use the invention within its fully claimed scope.

**The Existence of Working Examples**

Example 1 demonstrates the preparation of recombinant sendai viruses comprising transgenes, wherein the transgenes are placed between R1 and R2 of the sendai virus genome. Example 2 demonstrates that GFP transgenes of these recombinant sendai viruses are infective in nerve cell lines and express GFP. Example 3 demonstrates the culture of rat primary nerve cells. Example 4 demonstrates the infectivity and expression GFP transgenes in recombinant sendai viruses used to transform the rat primary nerve cells. Example 5 demonstrates that human fibroblasts deficient in beta-glucuronidase can be infected with recombinant sendai viruses carrying the beta-glucuronidase transgene and express the transgene. Example 6 demonstrates the expression of GFP in the brains of mice after stereotactic injection of recombinant sendai viruses carrying the GFP transgene. Example 7 demonstrates a similar expression of GFP after stereotactic injection to another position within the brains of mice and rats. Example 8 demonstrates that knock-out mice for the beta-glucuronidase gene exhibit slight recovery after

stereotactic injection of recombinant sendai viruses carrying the beta-glucuronidase transgene, and that such is associated with the expression of the transgene. Example 9 demonstrates that gerbils and mice stereotactically injected in the brain with recombinant sendai vectors carrying the FGF-1 or FGF-9 transgene exhibit a temporary decrease in body weight, while vectors carrying the GFP transgene exhibited no such weight decrease. Examples 10 and 11 demonstrate that gerbils stereotactically injected into the brain with recombinant sendai virus comprising the FGF-1 or GDNF transgene exhibit less ischemia upon subsequent ischemic insult than gerbils not so treated. In addition such is associated with less apoptosis 3-5 days after the ischemic insult.

While Applicant has demonstrated reasonably predictable use of sendai vectors comprising beta-glucuronidase, FGF-1, FGF-5, GDNF, or GFP, for treating beta-glucuronidase deficient mice, weight control, protection against ischemic insult, and diagnostic uses, in gerbils, mice and rats, the Artisan could not reasonably predict that any paramyxoviridae virus would be effective, that any route of administration would be effective, that *ex vivo* therapy would be effective, that any transgene could be used, or that animals outside of rodents could be treated, in view of the other factors reviewed above.

**The Quantity of Experimentation Needed to Make and/or Use the Invention**

Because of the insufficiency of working examples, insufficient guidance and direction provided by Applicant, the inherent unpredictability in the art, the state of the art, and the nature of the invention, even in the face of an advanced level of skill in the art, the Artisan would have been required to perform a large amount of experimentation to make and/or use the invention within its fully-claimed scope.

Such experimentation would be required to determine which paramyxoviridae viruses would be effective vectors, where to place the transgene in any particular virus, which transgenes would produce any particular effective therapy, which cells transformed with the virus could be used to transform other cells, both *in vivo* and *in vitro*, and to determine which animals, outside rodents, could be treated by any particular method of administration.

**Conclusion**

Because of the large amount of experimentation required to make and/or use the invention within its fully claimed scope, as claimed by Applicant, such experimentation is considered undue and therefore, the claims are not enabled for their fully claimed scope.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Hasan, et al. (1997) J. Gen. Virology, 78: 2813-20.

Claim 16 encompasses any paramyxoviridae virus vector. Intended use is not considered limiting for purposes of product claims and art rejections. Hasan teaches Sendai virus vectors comprising firefly luciferase transgenes (ABSTRACT).

**With regard to the following rejection, the Examiner was unable to obtain a copy of the U.S. patent which has issued from the same application as the following Pregrant Publication. Therefore, Applicant is forewarned that the following rejections may be held in light of that patent (U.S. Patent No. 6,723,532 filed 13 September 2001, patented 20 April 2004, and claiming Priority to PCT/JP96/03068, filed 22 October 1995).**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 16 is rejected under 35 U.S.C. 102(e) as being anticipated by Patent Application Publication No.: US 2002/0100066 to Nagai, et al., filed 13 September 2001, published 25 July 2002, and claiming priority to Japanese application number 7/308315, filed 31 October 1995.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim 16 encompasses any paramyxoviridae virus vector. Intended use is not considered limiting for purposes of product claims and art rejections. Nagai teaches recombinant

paramyxoviridae virus vectors comprising mutations or deletions of certain endogenous genes (p. 5, paragraph 0104) and the insertion of exogenous genes (p. 5, paragraph 0109).

Claim 16 is rejected under 35 U.S.C. 102(e) as being anticipated by Patent Application Publication No.: US 2002/0098576 to Nagai, et al., filed 1 December 2000, Published 25 July 2002, and claiming priority to Japanese Application 7/285417, filed 1 November 1995.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim 16 encompasses any paramyxoviridae virus vector. Intended use is not considered limiting for purposes of product claims and art rejections. Nagai teaches recombinant Sendai virus vectors which may comprise deletions of endogenous genes (p. 3, paragraph 0039) or incorporation of exogenous genes (p. 4, paragraph 047).

## CONCLUSION

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER